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Effects of Long-Term α-Tocopherol Supplementation on Serum Hormones in Older Men

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BACKGROUND. α-tocopherol supplementation significantly reduced risk of prostate cancer in the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study. Sex hormones are thought to be involved in the etiology of prostate cancer. We examined whether long-term supplementation with α-tocopherol modified serum hormone levels.
METHODS. Men who were cancer-free consumed $\geq 90\%$ of the study capsules, and who had both baseline and follow-up blood available, were eligible for the study. One hundred men who received α-tocopherol were matched on age, study center, and length of time between blood draws to 100 men who received a placebo. Multivariate linear regression models which allowed for a separate intercept for each matched pair were used to evaluate the effect of α-tocopherol supplementation on follow-up hormone concentrations.
RESULTS. Compared to men who received a placebo, we found significantly lower serum androstenedione ($P = 0.04$) and testosterone ($P = 0.04$) concentrations among men who received α-tocopherol, after controlling for baseline hormone level, follow-up serum cholesterol concentration, body mass index, smoking, and fasting time. Geometric mean (95% confidence interval; CI) androstenedione concentration among men who received α-tocopherol was 145 ng/dl (CI, 137–153) after adjusting for covariates, compared to 158 ng/dl (CI, 148–167) among men who received a placebo. Mean testosterone concentrations for men who received α-tocopherol and placebo were 539 (CI, 517–562) and 573 (CI, 549–598) ng/dl, respectively.
CONCLUSIONS. These results suggest that long-term α-tocopherol supplementation decreases serum androgen concentrations, and could have been one of the factors contributing to the observed reduction in incidence and mortality of prostate cancer in the α-tocopherol treatment group of the ATBC Study. *Prostate 46:33–38, 2001.* © 2001 Wiley-Liss, Inc.

KEY WORDS: **vitamin E; sex hormones; vitamin supplements**

INTRODUCTION

In the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study, supplementation with α-tocopherol (vitamin E) resulted in a 32% reduction in the incidence and a 41% reduction in the mortality [1,2] of prostate cancer. The mechanism through which this vitamin may have affected prostate

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carcinogenesis is not known; however, alteration of sex hormones is among the stronger hypotheses for this hormone-dependent site. Although results of epidemiologic studies of serum hormones in relation to prostate cancer are inconsistent, [3] in the largest prospective analysis to date, Gann et al. [4] reported a significant positive association for testosterone with prostate cancer risk. Dorgan et al. [5], in a nested case-control study of 116 prostate cancer cases from the ATBC study cohort, found no strong relation between baseline serum androgens and estrogens and prostate cancer overall. However, intervention groups significantly modified the association of serum androstenedione concentration with risk of prostate cancer. Among men who did not receive α-tocopherol, there was a tendency for serum androstenedione concentration to be positively associated with prostate cancer risk, whereas among men who received α-tocopherol, the converse was observed. In that analysis we did not have the opportunity to evaluate whether serum hormone concentration was altered by the α-tocopherol intervention.

Prolactin, a pituitary hormone, stimulates the proliferation and differentiation of prostate cells and potentiates the action of androgens in animal models [6]. Increased prolactin levels have been observed in men with prostatic carcinoma [6]. However, the exact role of prolactin in prostate carcinogenesis is still unclear. Animal work has suggested that α-tocopherol could reduce prolactin secretion [7].

We previously demonstrated an inverse relationship between baseline serum α-tocopherol and serum androstenedione, testosterone, sex hormone-binding globulin (SHBG), and estrone [8]. In the present study, we evaluated whether long-term α-tocopherol supplementation modified serum sex hormone concentrations during follow-up in the ATBC Study.

MATERIALS AND METHODS

Study Participants

The ATBC Study was a large, randomized, double-blind, placebo-controlled prevention trial to determine whether daily supplementation with α-tocopherol, β-carotene, or both would reduce the incidence of lung or other cancers. The study was conducted in Finland between 1985–1993 as a joint project between the National Public Health Institute in Finland and the U.S. National Cancer Institute. The design, methods, and initial results of the ATBC Study, have been published [7,9]. Briefly, 133 male smokers between ages 50–69 were recruited from southwestern Finland between 1985–1988 and randomly assigned to one of four groups, based on a 2×2 factorial design. Men who had prior cancer, had a serious illnesses, or reported current use of vitamins E (>20 mg/day), A ($>20{,}000$ IU/day), or β-carotene (>6 mg/day) were ineligible. All study participants provided informed consent. Participants received 50 mg/day α-tocopherol (as *dl*-α-tocopheryl acetate), 20 mg/day β-carotene, both α-tocopherol and β-carotene, or placebo. Active follow-up continued for 5–8 years until April 30, 1993.

The study sample for this analysis consisted of trial participants who had not been diagnosed with cancer, and who had both baseline and follow-up blood available. The time between the two blood draws ranged between 2.0–6.7 years, with a median of 3.7 years. Only men who had provided early-morning blood samples (before 10 AM) and had consumed 90% of the study capsules were eligible. Sample size calculations based on our previous cross-sectional hormone data suggested that 200 subjects would be adequate numbers for a matched comparison. One hundred participants who met the above criteria and had received only α-tocopherol supplementation were randomly selected and matched to 100 randomly selected men who had received a placebo on age (± 1 year), study center, and length of time between blood collections.

Data Collection

At baseline, study participants completed a social and general medical history questionnaire and a food frequency questionnaire, and height and weight were measured. Participants made three follow-up visits annually and provided information on their health, use of nontrial vitamin supplements, and smoking habits since the last visit. Blood was collected from all of the trial participants at baseline. From the second year of the trial onward, one sample of blood was taken from an annual random sample of 700–800 participants on the day they visited the study center. Repeated serum samples were not available; however, all blood was collected in the morning, before 10:00 AM, to minimize the effects of diurnal variability. Participants were asked to fast overnight; data on fasting time was recorded in hours. Serum was separated into 1-ml aliquots and immediately stored in glass vials at -70°C.

Baseline and follow-up serum samples for each matched pair were positioned next to each other within batches for analysis. Five samples were broken either in transit or during thawing and were unavailable for analysis. Testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), prolactin,

and SHBG were measured by Endocrine Sciences, Inc. (Calabasas Hills, CA), using standard procedures. Testosterone was extracted and purified by column chromatography, and then measured by radioimmunoassay (RIA). The percent of testosterone that was bioavailable was determined by ammonium sulfate separation of the SHBG-bound steroid from albumin-bound and free steroid. Bioavailable testosterone concentration was derived from the product of the total serum testosterone and the percent non-SHBG-bound testosterone. The binding capacity of SHBG was directly measured in serum. Androstenedione was measured by RIA after extraction with hexane and ethyl acetate and separation from the aqueous phase by centrifugation. DHEAS was subjected to enzyme hydrolysis and measured directly by RIA. Prolactin was measured by a chemiluminescent monoclonal antibody method. The overall coefficients of variation for the sex hormones were as follows: testosterone, 9.0%; bioavailable testosterone, 13.3%; androstenedione, 12.8%; DHEAS, 12.1%; prolactin, 9.2%; and SHBG, 24.0%. With the exception of the SHBG assay, these were all within the acceptable range. Problems associated with the SHBG assay did not affect the bioavailable testosterone results, since SHBG concentrations were not used to estimate bioavailable testosterone concentrations. Serum α-tocopherol was measured enzymatically (Boehringer Mannheim, Mannheim, Germany) [10] in the chemistry laboratory of the National Public Health Institute (Helsinki, Finland), with a between-run coefficient of variation of 2.2%.

Statistical Analysis

The serum hormone concentrations were log-transformed to normalize their distributions prior to analysis. All values were plotted and examined for outliers. Two influential outliers were omitted prior to analysis. Multivariate linear regression models which allowed for a separate intercept for each matched pair were used to evaluate the association of α-tocopherol supplementation with follow-up hormone concentrations. For each hormone, a model was defined with follow-up log hormone concentration as the dependent variable and α-tocopherol supplementation status (yes/no) as an independent variable. Baseline hormone level, follow-up serum total cholesterol concentrations, body mass index (BMI), number of cigarettes smoked per day, and fasting time were also included in models as independent covariates. Physical activity, and dietary intake variables, including energy, fat, cholesterol, fiber, vitamin C, and α-tocopherol intake, did not modify the associations between serum α-tocopherol and sex hormones and were not included in the models. Analysis of covariance was used to generate the geometric means of hormone concentrations by supplementation status after adjusting for covariates. Effect modification by age, BMI, serum cholesterol, energy intake, smoking, treatment time, initial hormone status, and alcohol intake was assessed by including factors and their cross-product terms with the treatment group variable in multivariate linear regression models or by stratified analysis. For subgroup analyses, variables of interest were stratified at the median, and the data were analyzed as unmatched, controlling for the matching factors in the models. Statistical analyses were performed using Statistical Analysis Systems (SAS) software [11, 12].

RESULTS

Table I shows the aggregate group means for selected participant characteristics by intervention group. At baseline, there were no significant differences by intervention group for any of the participant characteristics or for any of the serum hormone concentrations (unpaired data). There was a 50% increase in serum α-tocopherol in the supplemented group after nearly 4 years on-study, compared to an 8% increase in the placebo group.

Mean follow-up serum hormone concentrations (with 95% confidence intervals) by α-tocopherol supplementation adjusted for relevant covariates are shown in Table II. In multiple regression analyses after adjusting for covariates, men who received α-tocopherol supplementation had significantly lower follow-up androstenedione and testosterone concentrations. Androstenedione was 8% and testosterone 6% lower in the α-tocopherol group at follow-up as compared to the placebo group, with smaller nonsignificant decrements seen for the other sex hormones.

We did not observe any meaningful effect modification of the α-tocopherol-hormone associations by BMI, physical activity, serum cholesterol, energy intake, smoking, treatment duration, or baseline hormone concentration in these data. There was a suggestion of effect modification by alcohol intake for the association between α-tocopherol and testosterone ($P = 0.09$), with α-tocopherol supplementation leading to lower concentrations of testosterone among men consuming less as opposed to more alcohol.

DISCUSSION

In this group of male smokers, after accounting for potential confounders, men who received long-term

TABLE I. Characteristics of Study Participants

	Treatment group			
	Placebo ($n = 100$) mean	(S.D.)	α-tocopherol ($n = 100$) mean	(S.D.)
Characteristics				
Age (years)	55.3	(4.4)	55.1	(4.4)
Height (cm)	174.2	(6.1)	174.2	(5.8)
Weight (kg)	78.3	(13.6)	80.7	(12.4)
BMI (kg/m^2)	25.8	(4.2)	26.5	(3.7)
Cigarettes (no./day)	20.5	(8.6)	20.4	(8.0)
Dietary intake				
Energy (kcal)	2,882.0	(746)	2,917.0	(880)
Fat (g)	124.0	(38)	127.0	(46)
Fiber (g)	26.6	(10.2)	26.6	(9.7)
Alcohol (g)	17.5	(20.9)	16.4	(17.2)
Vitamin E (mg)	17.6	(22.7)	14.6	(11.1)
Years between blood draws	3.9	(1.3)	3.9	(1.3)
Serum values				
Total cholesterol (mmol/l)[a]				
Baseline	6.1	(1.2)	6.3	(1.2)
Follow-up	5.9	(1.2)	6.0	(1.0)
α-tocopherol (mg/l)[a]				
Baseline	11.7	(1.3)	11.7	(1.3)
Follow-up	12.6	(1.3)	17.5	(1.3)
Hormones (baseline/follow up)[a]				
Androsenedione (ng/dl)	150	(1.3)	148	(1.3)
	154	(1.4)	148	(1.4)
DHEAS (μg/dl)	150	(1.7)	141	(1.7)
	125	(1.8)	120	(1.8)
Prolactin (ng/ml)	6.0	(1.6)	6.9	(1.7)
	7.8	(1.6)	8.3	(1.7)
SHBG (μg/ml)	1.2	(1.6)	1.0	(1.7)
	1.2	(1.5)	1.0	(1.6)
Testosterone (ng/dl)	579	(1.4)	557	(1.4)
	574	(1.4)	542	(1.4)
Biotestosterone (μg/dl)	170	(1.4)	171	(1.4)
	164	(1.3)	162	(1.4)

[a] Geometric means and standard deviations (SD) shown for serum factors.

TABLE II. Geometric Means (95% CI) of Follow-Up Hormone Serum Concentration by Treatment Group After Adjusting for Covariates*

	Placebo		α-tocopherol		*P*-value
Androstenedione (ng/dl)	158	(148, 167)	145	(137, 153)	0.04
DHEAS (μg/dl)	130	(121, 140)	121	(113, 130)	0.18
Prolactin (ng/ml)	8.4	(7.7, 9.1)	8.0	(7.3, 8.7)	0.44
SHBG (μg/dl)	1.19	(1.13, 1.24)	1.13	(1.08, 1.19)	0.19
Testosterone (ng/dl)	573	(549, 598)	539	(517, 562)	0.04
Bioavailable testosterone (μg/dl)	167	(159, 176)	161	(153, 169)	0.33

*Models adjusted for baseline serum hormone concentration, follow-up serum cholesterol concentration, and BMI, smoking, and fasting time. Matched on age, clinical center, and time between blood draws.

α-tocopherol supplementation had significantly lower serum testosterone concentrations as compared to men who received a placebo. Androstenedione, the major precursor for testosterone, also was significantly lower among men who received α-tocopherol supplements. Supplementation with α-tocopherol, together with the other covariates, predicted 85% and 70% of the variability in follow-up hormone concentrations for testosterone and androstenedione, respectively.

There is evidence that α-tocopherol may play a role in hormone metabolism. The adrenal, and to a lesser extent the testes, are the primary sources of androstenedione, and the testes secretes most of the testosterone in serum. High levels of α-tocopherol have been reported in the adrenal cortex, testes, and prostate, and α-tocopherol binding sites have been found in adrenal cell membranes [13]. Results of the current study are consistent with our previous findings of inverse associations between serum α-tocopherol with testosterone and androstenedione. In a cross-sectional analysis of 204 ATBC Study participants, we showed that baseline serum α-tocopherol concentration was significantly inversely related to baseline levels of serum androstenedione, testosterone, SHBG, and estrone [8]. In contrast to our results, in a hospital-based study, researchers supplemented 11 men aged 30–69 with 438 mg/day α-tocopherol for 8 weeks and reported a significant increase in plasma testosterone levels [14]. Unfortunately, because no control group was included in this study, it is possible that other factors may have contributed to these results. In another trial, 200 subjects given 600 IU/day *dl*-α-tocopheryl acetate for 4 weeks showed significant decreases in serum thyroid hormone levels [15]. While no sex hormone concentrations were measured in this study, administration of triiodothyronine (T3) has been shown to significantly increase serum testosterone levels [16]. In a controlled feeding trial, Bhathena et al. [17] fed 40 men 15 g/day of fish oil and fish oil supplemented with 200 mg vitamin E/day each for 10-week periods. Decreases in insulin, DHEAS, and growth hormone were observed during the vitamin E supplementation period. Other hormones were not measured, but decreased levels of insulin have been associated with lower testosterone levels by others [18]. In the present study, a 50-mg/day α-tocopherol supplement administered over 2 or more years was not associated with follow-up serum DHEAS concentrations. These studies, as well as our own, were based on single serologic measurements. This is likely to bias results toward a null funding because of potential increases in measurement error without pooled samples.

Few reports have addressed potential mechanisms through which α-tocopherol may have influenced serum sex hormone concentrations. It is possible that α-tocopherol modifies the synthesis, release, or clearance of sex hormones; however, there are very few data available to support these mechanisms. Some available information suggests that α-tocopherol could influence serum sex hormone concentrations through a prostaglandin-mediated mechanism. A role for prostaglandin PGE2 in maintaining the growth of malignant prostatic tissues has been suggested [19]. Prostaglandins stimulate secretion of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and adrenocorticotropic hormone (ACTH) [20–22], which in turn stimulate androgen production by the testes and adrenal cortex. In animals [23–26] and in cultured cells [27,28], supplementation with α-tocopherol beyond levels required for adequate nutrition inhibits prostaglandin PGE2 synthesis and downregulates both phospholipase A2 and cyclooxygenase [29], enzymes involved in the synthesis of prostaglandins from arachidonic acid. Consequently, higher serum α-tocopherol could potentially decrease enzyme activity involved in prostaglandin production, lower levels of PGE2 and other prostaglandins, and ultimately reduce levels of serum androgens. We were not able to test this hypothesis because cyclooxygenase mRNA expression and prostaglandins cannot be measured in previously frozen serum. Future studies to examine the effect of supplemental α-tocopherol on prostaglandin synthesis and the enzymes involved in sex hormone metabolism in tissues and on serum PSA concentrations may be warranted. Other studies to evaluate the effects of changes in serum sex hormones on serum growth factors or on tissue hormone concentrations may also be of interest.

In conclusion, compared to men who received a placebo, we found lower serum testosterone and lower androstenedione levels among men who received α-tocopherol supplementation. These results may have implications for the observed protective effect of supplemental α-tocopherol in relation to prostate cancer in the ATBC Study [2]. Research to identify additional mechanisms of α-tocopherol action could lead to an increased understanding of the etiology of prostate cancer.

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